PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	03.06.2004
Applicant's or agent's file reference PG4798	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/06415	18.06.2003	19.06.2002

Applicant
SMITHKLINE BEECHAM CORPORATION et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Ambroa, J.R. Tel. +49 89 2399-8012

Form PCT/IPEA/416 (January 2004)

Express Mail Label No.
EV 332064178 US

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PG4798	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/06415	International filing date *(day/month/year)* 18.06.2003	Priority date *(day/month/year)* 19.06.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/44, A61K31/44		
Applicant SMITHKLINE BEECHAM CORPORATION et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29.12.2003	03.06.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Schmid, J-C Telephone No. +49 89 2399-8347

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/06415

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-142 as originally filed

Claims, Numbers

1-21 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. (1-12,16-21) all partly

   because:

   ☒ the said international application, or the said claims Nos. 20,21 (IA) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. (1-12,16-21) all partly

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	14,15
	No:	Claims	1-13, 16-21
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-21
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	

2. Citations and explanations

   see separate sheet

SECTION III

Claim 20 and 21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

SECTION V

Reference is made to the following documents:

D1: WO 99 11255 A (ONO PHARMACEUTICAL CO., LTD.) 11 March 1999

D2: WO 00 64876 A (MCGEEHAN GERARD M ;MORRIS ROBERT (US); ZHANG LITAO (US); BOBKO MAR) 2 November 2000

D3: EP-A-1 067 109 (ONO PHARMACEUTICAL CO) 10 January 2001

D4: WO 97 31907 A (CALLAGHAN JOHN MARK O ;GLAXO GROUP LTD (GB); COBB JEFFREY EDMOND 4 September 1997

D5: EP-A-1 132 376 (TAKEDA CHEMICAL INDUSTRIES, LTD., JAPAN) 12 September 2001

D6: GENTLES, ROBERT G. ET AL: 'Standardization Protocols and Optimized Precursor Sets for the Efficient Application of Automated Parallel Synthesis to Lead Optimization: A Mitsunobu Example' JOURNAL OF COMBINATORIAL CHEMISTRY (2002), 4(5), 442-456 , XP002255800

D7: EP-A-1 283 039 (TAKEDA CHEMICAL INDUSTRIES, LTD., JAPAN) 12 February 2003 (2003-02-12) & WO 01 087293 A 22 November 2001

D8: WO 01 36351 A (LEWIS RONALD D II ;CORVAS INT INC (US); DUNCAN DAVID F (US); MADIS) 25 May 2001 (2001-05-25)

D9: KUCHAR M ET AL: 'BENZYLOXYARYLALIPHATIC ACIDS: SYNTHESIS AND QUANTITATIVE RELATIONS BETWEEN STRUCTURE AND ANTIINFLAMMATORY ACTIVITY' COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS, ACADEMIC PRESS, LONDON, GB, vol. 47, 1982, pages 2514-2524, XP001002034 ISSN: 0010-0765

D10: KUCHAR M ET AL: 'THE EFFECTS OF LIPOPHILICITY ON THE INHIBITION OF DENATURATION OF SERUM ALBUMIN AND ON THE ACTIVATION OF FIBRINOLYSIS OBSERVED WITH ASERIES OF BENZYLOXYARYLALIPHATIC ACIDS' COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS, ACADEMIC PRESS, LONDON, GB, vol. 48, 1983, pages 1077-1088, XP001002033

D11: US-A-4 221 919 (GRIMOVA JAROSLAVA ET AL) 9 September 1980 (1980-

09-09)

1). The subject-matter of claims 1-5 and 16-21 lacks novelty with respect to D1 (see D1, tables 26, 27 and 30).
The subject-matter of claims 13-15 is novel over D1 on account of the biphenyl, pyrimidylphenyl, pyridylphenyl or pyridazinylphenyl moiety of the derivatives of claims 13 -15.
The subject-matter of claims 1-13 lacks novelty with respect to reference example 1 of D5 and reference example 4 of D7 (see D5, page 37, lines 1-24; D7, page 27, lines 39-56) and with respect to generic formula (IV) of D5 and D7 (D5, page 18, lines 1-9; D7, page 21, line 5).
The subject-matter of claims 1-12 lacks novelty with respect to D8-D11 (see D8, claim 1, examples 3,4, figures 1C, 2K, 2V; D9 and D10, examples; D11, column 1, lines 20, examples).
The subject-matter of the present claims represent a novel selection over the compounds of formula (I) generically disclosed in D2, in particular novel combination A is a chemical bond with a=b=0).
The subject-matter of the present claims represents a novel selection over the compounds of formula (I) generically disclosed in D3.
The moieties bearing X and X' are attached in positions 1 and 4 of the phenyl ring, while R^4 is attached in a non specified position in formula (I) of D3. Preferably R^4 is attached preferably in position 3 (see D3; page 13, line 25; page 32, table 17).
The subject-matter of the present claims is novel over D4 on account of the radical R^1 and R^2 of the claimed derivative which represent H or C_1-C_3 alkyl as opposed to the radical Z for the corresponding derivatives of D4.

2). The technical problem underlying the application may be seen in the provision of further hPPAR activators.
D1-D3 which discloses derivatives having said activity are considered to represent the closest prior art.

As mentioned above, the compounds of present claims 13-15 represent a selection of a subgroup of compounds within the hPPAR activators generically disclosed in D1-D3.

Such a selection could be regarded as being inventive, if the selected derivatives

present unexpected effects or activities in relation to those described in the state of the art. However, no such effects or properties are indicated in the application. The closest compound of the prior art to be compared could be compound 1 of table 17 of D3 wherein the sole structural difference with a compound of claim 13 would be the position para opposed to meta.

At the present stage of the examining procedure, the subject-matter of claims 1 to 21 is judged to lack an inventive step (Article 33(3) PCT).